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| 09/722,010 | 11/27/2000 | Kuen Yong Lee | UMICH-9 | 4013 |

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| EXAMINER | |
|---|---|
| MAIER, LEIGH C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1623 | |

DATE MAILED: 07/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/722,010 | Applicant(s) Lee |
|---|---|---|
| | Examiner Leigh Maier | Art Unit 1623 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Mar 24, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1 and 3-22* is/are pending in the application.

4a) Of the above, claim(s) *19* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-5, 10-18, and 20-22* is/are rejected.

7) ☒ Claim(s) *6-9* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 8
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Status of the Claims*

Claim 2 has been canceled. Claims 20-22 have been added. Claims 1, 3, 4, 7-9, and 17 have been amended. Upon amendment, the search has been continued based upon another polysaccharide species, hyaluronic acid, as per the election of species requirement. Claims 1-18 read on the elected species. Claim 19 remains withdrawn from consideration as being drawn to a non-elected species. Any objection or rejection not repeated has been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 U.S.C. § 102*

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by PRESTWICH et al (US 5,874,417).

PRESTWICH discloses hydrazido-hyaluronate derivatives, in which the hydrazido moieties are considered to be sites of modification and crosslinkers. An exemplified species is further modified by a crosslinker, resulting in a hydrogel product that is 24% crosslinked. See Example 6. That would leave 76% of dangling hydrazide moieties. The example further discusses a product (hydrazido-HA:sulfo-EGS, bottom of col 32) in which the ratio of hydrazido-

HA to the bifunctional crosslinker is 1:0.36. This product is not fully characterized, but this reacion would result in a maximum of 72% crosslinking, with 28% dangling hydrazido moieties.

Evidence that the hydrazido reagents are considered both modifiers and crosslinkers is seen in Scheme B, bridging col 17-18.

***Claim Rejections - 35 U.S.C. § 103***

Claims 1, 3, 4, 13-15, 17, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over PRESTWICH et al (US 5,874,417).

The claims are drawn a hydrogel composition comprising a reversibly-crosslinked polysaccharide (hyaluronic acid) wherein the crosslinked product also has 20-90% dangling crosslinkers. Dependents further limit the amount of dangling crosslinkers, the shear modulus of the hydrogel, and recite a method for using the hydrogels for tissue engineering, cell transplantation, or drug delivery. Claim 17 is drawn to a hydrogel in which the crosslinked polysaccharide is more specifically described as modified by hydrazide groups and crosslinked with a compound having at least two aldehyde groups.

PRESTWICH teaches as set forth above. The reference further teaches that the object of the invention is to provide crosslinking is either reversible or irreversible. See col 2, lines 4-6. The reaction further teaches it use of dialdehydes as crosslinkers for HA functionalized with dihydrazido groups and also having pendant (dangling) hydrazido groups. See col 3-4. The pendant hydrazido groups allow for subsequent reactions, such as attachement of bioaffecting

agents. See col 5, lines 1-10 and col 6, lins 8-11. The refererence further teaches this type of attachment may occur before or after crosslinking. See col 10, lines 60-68. The reference further teaches that the thus prepared hydrogels have utility in drug delivery, tissue engineering, and cell transplantation. See col 14, lines 27-61. The reference does not specifically characterize crosslinked products having the full range of the percentage of dangling crosslinkers or the shear modulus of the prepared hydrogels. Neither does the reference specifically exemplify the use of a dialdehyde crosslinker.

It would have been obvious to one having ordinary skill in the art at the time the invention was to prepare the hydrogel compositions comprising crosslinked polysaccharides having the percentage of dangling crosslinker and initial shear modulus as that recited in the claims. As discussed above, the reference exemplifies a product having 76% dangling crosslinkers and another product which must have a minimum of 28% dangling crosslinkers. Therefore, the reference describes a range that is essentially the same as that recited in the claims. It would be within the scope of the artisan to optimize the percentage of dangling crosslinkers through routine experimentation. Although the reference is silent regarding the initial shear modulus of hydrogels prepared, these hydrogels would be expected to fall within the broad range recited in the claims because the reference teaches precisely the same utility as the instant invention. One of ordinary skill would reasonably expect success in administering these hydrogels for drug delivery, tissue engineering, and cell transplantation, as the reference teaches

that they have this utility. It would be further obvious to use a dialdehyde as the crosslinker with the hydrazido-HAs as the reference specifically suggests their use.

Claims 5, 10-12, 16, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over PRESTWICH et al (US 5,874,417) as applied to claims 1, 3, 4, 13-15, 17, and 20-22 above, and further in view of SPIRO et al (US 6,303,585) and MOONEY et al (WO 98/12228).

The invention is as set forth above. Dependents are drawn to the use of an oxidized polysaccharide (hyaluronic acid) wherein the polysaccharide is crosslinked with a dihydrazide, such as adipic acid dihydrazide. Claim 10 further limits the molecular weight of the polysaccharide is at or below the renal threshold of humans.

PRESTWICH teaches as set forth above. The reference does not specifically teach the use of an HA having molecular weight below the renal threshold, but the reference clearly suggests the use of lower molecular weight HA. See Example 1 and claim 2. The reference does not teach the use of oxidized HA.

SPIRO teaches the use of HA that is oxidized (to indroduce aldehyde groups) and crosslinked to prepare gels having utility in drug delivery, cell encapsulation, and tissue engineering. See col 3-5 and claims. The reference does not teach the use of adipic acid dihydrazide.

MOONEY teaches that in the preparation of hydrogels for use in cell transplantation, it is desirable to prepare the hydrogel comprising a polymer having a molecular weight less than .

about 30 kD to about 50 kD, so that it can be cleared through the kidneys. See page 8, lines 7-10. The reference further teaches the use of adipic acid dihydrazide for crosslinking a polyaldehyde polysaccharide for the preparation of a hydrogel having utility for drug delivery and cell transplantation. See example 19 and claims.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a hydrogel comprising a crosslinked polysaccharide having dangling crosslinkers as taught by PRESTWICH using oxidized HA crosslinked. One of ordinary skill would reasonably expect success in using this product, as SPIRO had taught that this HA has the same utility as PRESTWICH and the instant invention. It would be be further obvious to use AAD as the crosslinker and prepare a crosslinke HA having a molecular weight at or below the renal threshold, as MOONEY had taught that AAD has this utility, and a molecular weight at or below the renal threshold is desirable for a hydrogel used for cell transplantation. It would be within the scope of the artisan to optimize the percentage of dangling crosslinkers through routine experimentation.

***Conclusion***

Claims 6-9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

***Examiner's hours, phone & fax numbers***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (703) 308-4525. The examiner can normally be reached on Monday-Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (703) 308-4624, may be contacted. The fax phone number for Group 1600, Art Unit 1623 is (703) 308-4556 or 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-1235.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more.

Leigh C. Maier
Patent Examiner
June 28, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
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